

**INTERNATIONAL SEARCH REPORT**

International application No.

PCT/US04/36848

**A. CLASSIFICATION OF SUBJECT MATTER**

IPC(7) : A61K 35/14, 35/16; A23J 1/00; C07K 17/00  
 US CL : 530/384, 380, 412, 413, 414, 416, 417, 829, 830; 424/529, 530

According to International Patent Classification (IPC) or to both national classification and IPC

**B. FIELDS SEARCHED**

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 530/384, 380, 412, 413, 414, 416, 417, 829, 830; 424/529, 530

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

Please See Continuation Sheet

**C. DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No. |
|------------|--|-----------------------|
| Y          | HOFFER et al. Improved virus safety and purity of a chromatographically produced factor IX concentrate by nanofiltration. Journal of Chromatography B, 1995, Vol. 669, pages 187-196, especially pages 187-190 and Figures 1-5.                | 1-87 and 99-101       |
| Y          | LIM et al. Correlation between Mortality and the Levels of Inter-Alpha Inhibitors in Plasma of Patients with Severe Sepsis. The Journal of Infectious Diseases, 15 September 2003, Vol. 188, pages 919-926, especially pages 919, 920 and 925. | 1-87 and 99-101       |
| Y          | YANG et al. Administration of human inter-alpha-inhibitors maintains hemodynamic stability and improves survival during sepsis. Crit. Care. Med., 2002, Vol. 30, No. 3, pages 617-622, especially pages 617-621.                               | 1-87 and 99-101       |
| P, Y       | WU et al. Delayed administration of human inter-alpha inhibitor proteins reduces mortality in sepsis. Crit. Care. Med., 2004, Vol. 32, No. 8, pages 1747-1752, especially pages 1747-1751 and Figures 1-5.                                     | 1-87 and 99-101       |



Further documents are listed in the continuation of Box C.



See patent family annex.

|   |     |  |
|---|-----|--|
| • Special categories of cited documents:  | "T" | later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention  |
| "A" document defining the general state of the art which is not considered to be of particular relevance  | "X" | document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone   |
| "E" earlier application or patent published on or after the international filing date   | "Y" | document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | &   | document member of the same patent family  |
| "O" document referring to an oral disclosure, use, exhibition or other means  |     |  |
| "P" document published prior to the international filing date but later than the priority date claimed  |     |  |

Date of the actual completion of the international search

10 September 2005 (10.09.2005)

Date of mailing of the international search report

04 NOV 2005

Name and mailing address of the ISA/US

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**INTERNATIONAL SEARCH REPORT**International application No.  
PCT/US04/36848**C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

| Category * | Citation of document, with indication, where appropriate, of the relevant passages  | Relevant to claim No. |
|------------|---|-----------------------|
| A          | LIM et al. Affinity purification and enzymatic cleavage of inter-alpha inhibitor proteins using antibody and elastase immobilized on CIM monolithic disks. Journal of Chromatography A, 2005, Vol. 1065, pages 39-43. | 1-87 and 99-101       |

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**Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)**

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.:  
because they relate to subject matter not required to be searched by this Authority, namely:
  
2.  Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
  
3.  Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

**Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)**

This International Searching Authority found multiple inventions in this international application, as follows:  
Please See Continuation Sheet

1.  As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying additional fees, this Authority did not invite payment of any additional fees.
3.  As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
  
4.  No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.: 1-87 and 99-101

**Remark on Protest**

- The additional search fees were accompanied by the applicant's protest and, where applicable, the payment of a protest fee.
- The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.
- No protest accompanied the payment of additional search fees.

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**BOX III. OBSERVATIONS WHERE UNITY OF INVENTION IS LACKING**

This International Search Authority has found 4 inventions claimed in the International Application covered by the claims indicated below: This application contains the following inventions or groups of inventions, which are not so linked as to form a single general inventive concept under PCT Rule 13.1. In order for all inventions to be examined, the appropriate additional examination fees must be paid.

Group I, claim(s) 1-87 and 99-101, drawn to a process for producing a blood plasma-derived I-alpha-IP and P-alpha-I composition comprising a mixture of inter-alpha-inhibitor protein (I-alpha-I) and pre-alpha inhibitor) P-alpha-I), pharmaceutical and a kit formulation thereof and to a method of treating an inflammation related disorder, cancer and infectious disease in a subject.

Group II, claim(s) 88-95, drawn to a method of treating a subject for acute inflammatory disease by determining the pre-treatment level of inter-alpha inhibitor protein and administering an effective amount of I-alpha-IP to treat the subject.

Group III, claim(s) 96 and 97, drawn to a method for predicting a response to an I-alpha-IP therapy by assaying a sample of inter-alpha inhibitor proteins.

Group IV, claim(s) 98, drawn to a method for monitoring the progress of a subject being treated with an I-alpha-IP therapy by determining the pre-treatment level of inter-alpha inhibitor proteins and administering an effective amount of I-alpha-IP.

This International Searching Authority considers that the international application does not comply with the requirements of unity of invention Rules 13.1, 13.2 and 13.3) for the reasons indicated below:

The inventions listed as Groups I-IV do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: The methods of Groups I-IV each has different scope, they are directed to various methods of using the compositions (i.e., inter-alpha inhibitor proteins from human plasma) for different purposes. Although, inventions I-IV are related, the end results of the aforementioned treatment or prediction or monitoring are divergent and a search conducted for one would not necessarily overlap with a search conducted for another. Further, inventions I-IV each differ from the other in a method of treating an inflammation related disorder, cancer and infectious disease in a subject (Group I), a method of treating a subject for acute inflammatory disease (group II), a method for predicting a response to an I-alpha-IP therapy (Group III) and a method for monitoring the progress of a subject being treated with an I-alpha-IP therapy (Group IV). Thus, the various methods using the same compositions/formulations as recited above do not correspond to the same technical features and are not connected in design, operation or effect because they differ in method steps, parameters and reagents used, and as such, the methods as grouped are different from each other because they represent different technical features and different endeavors. Thus, the method of treating differs from the method for predicting or the method for monitoring and *vice versa* because the methods do not correspond to the same technical features and are not connected in design, operation or effect. Therefore, Groups I-IV do not share the same technical features, the inventions do not relate to a single inventive concept.

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**Continuation of B. FIELDS SEARCHED Item 3:**

APS, CAS Online, Medline, Embase, Bisis, WPIDS

search terms: blood plasma, inter-alpha inhibitory protein, pre-alpha inhibitory protein, purif? or produc? or mak? or isolat? or extract?, prothrombin, clotting factor IX or FIX or cryosupernatant or cryo poor plasma or cryoprecipitat?, amino-exchahnge chromatograph? diethylaminoethyl-dextran or DEAE Sephadex, Toyopearl, ion oranion or cation exchange, treat? or ameliorat? or therapeut? inflammat? or disorder? or sepsis or cancer